The Office Action fails to comprehend the purpose and function of a vaccine when it asserts that Claim 1 is vague and indefinite because it recites "in an amount sufficient to confer immunity to Group A streptococcal infection." This lack of understanding is evident when the Office Action inquires as to whether therapeutic or therapeutically effective amounts are involved.

Strictly speaking, a vaccine is not a therapeutic agent. Although some vaccines may facilitate rapid therapeutic results, vaccines are not generally administered as therapeutic agents. Instead, a vaccine is a preventative agent which acts by conferring immunity against a specific pathogen or class of pathogens. Therefore, there is no therapeutic amount of vaccine to be administered. Claim 1 uses the language "amount sufficient to confer immunity" to indicate the proper target for vaccine dosage. Claim 1 therefore instructs the skilled artisan that the vaccine must contain enough cystein protease to invoke a protective immune response in the patient.

The Claim language does not need to indicate a recipient of the claimed immunity. As the Office Action admits on pages 2-3, the specific dosage of a vaccine can be "determined by one of skill in the art." Therefore, Claim 1 cannot be indefinite for use of "an amount sufficient to confer immunity," because a skilled artisan can readily determine the amount for an intended recipient.

Nor is Claim 1 vague and indefinite for use of the term "conserved cysteine protease." The Office Action fails to understand the definition and proper use of the terms protease, protein, peptide and purified protein.

The term "peptide" refers to a compound formed by the joining together of <u>two or more</u> amino acids through amide bonds (See e.g. Kilgour p. 352; Durland's Illustrated

Medical Dictionary p. 1158; both attached). The skilled artisan readily understands that a "peptide" is a small protein, or a piece of a protein, usually consisting of a chain of 20 or fewer amino acids. Claim 1 claims a "conserved cysteine proteas ." The t rm "prot in" generally is understood to refer to a polypeptide chain containing more than 20 amino acids. The term protease describes a molecule capable of hydrolyzing peptide bonds in a protein or peptide. A protease may be longer, or shorter than 20 amino acids, therefore the term "protease" can encompass both proteins and peptides. Applicants claim a protease, and are not required to select between the terms protein and peptide.

Furthermore, a protease is only one type of protein or peptide, therefore, "protease" is actually a narrower description than protein or peptide. A skilled artisan readily understands the definition of a protease. Additionally, use of the term "cysteine" further narrows that type of protease claimed. The Office Action would improperly require Applicants to apply broader terms, in order to make their claim less "vague and indefinite."

Applicants do not need to recite that the vaccine is "being administered to" in order to make the intended use functional. Applicants respectfully assert that the skilled artisan understands the term "vaccine" refers to the particular preparation intended for administration. For example, a skilled artisan, and even perhaps a layperson, would understand that a vial of smallpox or flu materials useful as an immunization agents contains "vaccines" without the necessity of reciting its intended use. A vaccine, as used in Applicants' claim, is a noun that does not require a recitation of its intended use to define its meaning. Contrary to the Office Action's assertion, the term vaccine does carry considerable patentable weight.

The Office Action again errs when it asserts that "a physiologically acceptable non-toxic vehicle is undefined technology." The skilled artisan readily understands that a vehicle for a vaccine is the excipient or formulation for the active ingredient of the vaccine. An adjuvant is merely one functional type of vehicle, the term vehicle refers to the pharmaceutical formulation of the vaccine. Dorland's Illustrated Medical Dictionary defines a vehicle as an excipient (See p. 1695; attached). An excipient is any more or less inert substance added to a prescription in order to confer a suitable consistency or form to the drug. (See Dorland's Illustrated Medical Dictionary at p. 555; attached). The skilled artisan understands that a multitude of vehicles are possible. Therefore, the term, "physiologically acceptable non-toxic vehicle" is readily recognized by the skilled artisan.

The Office Action is also mistaken when it asserts that the language in Claim 2, "cysteine protease is a streptococcal pyrogenic exotoxin B or fragments," is vague and indefinite. Streptococcal pyrogenic exotoxin B is known in the art as the term for a cysteine protease produced by *S. pyrogenes*. A skilled artisan would readily recognize that the speB detailed throughout Applicant's specification refers to Streptococcal pyrogenic exotoxin B. Furthermore, the speB gene is well known in the art and the skilled artisan recognizes that Applicants are referring to the protein product of the speB gen .

Applicants also point out that the term fragment is not indefinite. The term as used clearly indicates that a fragment is a smaller piece of the whole. Therefore, it is readily ascertainable that Applicants refer to a piece from the whole of Streptococcal pyrogenic exotoxin B.

In light of the above remarks, Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 102(a)

Claims 1-4 are rejected und r 35 U.S.C. §102(a). The Office Action asserts that Applicants' invention is anticipated by *Kapur et al.*, Microbial Pathogenesis, 15:327-346, 193, ("*Kapur I*") and *Kapur et al.* PNAS, 90:7676-7680, August 1993, ("*Kapur II*"). Applicants respectfully assert that in view of Applicants' remarks regarding the Section 112 rejection and the additional remarks to follow, that *Kapur I* & *Kapur II* do not anticipate Applicants' invention. Applicants' invention is not anticipated because the cysteine protease claimed by Applicants is not the same product taught by both *Kapur* references.

As discussed in the preceding Section 112 argument, the Office Action fails to appreciate the definition and construction of a vaccine. This misconception also permeates the Office Action's comments regarding the Section 102(a) rejection. *Kapur I* & *Kapur II* teach only the purification and partial amino acid sequencing respectively, of a *S. pyrogenes* cysteine protease, they do not teach the use of any cysteine protease as a vaccine. In fact, *Kapur I* teaches that "[A]n efficacious vaccine is not yet available for *S. pyrogenes*." *Kapur I* leaves little doubt that it does not anticipate Applicants' invention when it indicates that the knowledge that a cysteine protease is involved may have significant implications for vaccine research. This statement conclusively establishes that *Kapur I* does not teach a vaccine and that Kapur, as a skilled artisan, recognizes that mere isolation and characterization of a protein is insufficient to yield a vaccine.

It remains important to continue to recognize that Applicants claim a vaccine, and not simply the product of a protein purification scheme. The skilled artisan readily recognizes that the mere isolation or purification of a protein related to a bacterial infection is insufficient to yield a vaccin . This point is even more important wh n the protein

involved is directly responsible for th pathogenicity of the bacterium. Cysteine protease cannot b administered in a native form as a vaccine because the active enzyme will act as a toxin. Nor is it possible to randomly denature the protein and administer the denatured protein as a vaccine because the protein must at least a portion of its original, native three-dimensional structure. This retention of structure is necessary so that the vaccine may induce immunity against the native three dimensional structure that is secreted by the bacterium *in vivo*. Therefore, the creation of a vaccine is not automatic or assured, even if the amino acid sequence of the antigen is known. The current difficulties with obtaining a functional vaccine against the AIDS virus is a perfect example of this principle.

Applicants, in teaching and claiming a vaccine are not claiming the product of purification of cysteine proteases. Applicants are claiming a vaccine, which is the end product of controlled processing of a cysteine protease. This processing is analogous to the creation of a diamond. A diamond is not the same product as the carbon from which it is made. Similarly, Applicants' vaccine is the product of a change in the structural conformation of the original molecule. As mentioned previously, the toxic cystein protease must be converted to a non-toxic form. This process involves inactivating the native form of a cysteine protease so that the proteolytic activity is removed. Therefore, the inactivated cysteine protease (the vaccine) has a different three-dimensional structure compared to the native protein. Applicants' claim language specifying a non-toxic vehicle specifically excludes native (ie. active) cysteine proteases.

At the other end of the spectrum, total denaturation of the cysteine protease will not necessarily lead to a vaccine because the cysteine prot ase must retain enough of its

original three dimensional structure to stimulate an immunological response directed against the cysteine proteas produced *in vivo* by the bacteria. Therefore, disclosure of the protein amino acid sequence and the purification scheme will still not predictably and reliably lead to the production of a vaccine. In light of these facts, it is clear that the two *Kapur* references do not teach each and every limitation of Applicants' invention.

Under the Office Action's misinterpretation, no vaccine would be patentable if the antigen had ever been identified or purified. This error denies the processes and work involved in creating a vaccine. The inventive originality in the case of a vaccine is the discovery or creation of a processed form of the antigen, suitable to invoke an immune response without exhibiting the toxic effects of the disease.

In light of the above remarks, Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 102(b)

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as anticipated by *Tal et al.*, or *Hauser et al.*, or *Gerlach et al.* None of these references teach a vaccine. *Hauser et al.* reports a determination of the molecular weight of Group A Streptococcal infection exotoxin type B and its relationship to other pyogenic toxins and to streptococcal proteinase inhibitors. The *Gerlach et al.* reference presents a chemical and serological study of erythrogenic toxin type B. *Tal et al.* reports the complete amino acid sequence of streptococcal proteinase. Applicants again respectfully assert that disclosure of a protein sequence does not anticipate the invention of a vaccine.

None of these references disclose the use of cysteine protease as a vaccin against Group A Streptococcal infection. As mentioned previously in this r sponse, the mere isolation or characterization of a protein (or its nucleic acid precursor) is insufficient to yield a vaccine. Isolation of the protein is not predictive of the likelihood of success of obtaining a functional vaccine.

In light of the above remarks, Applicants respectfully request that these rejection be withdrawn.

35 U.S.C. § 103(a)

Claim 5 is rejected as unpatentable over *Kapur* I, or *Kapur II*, or Gerlach *et al.*, or *Hauser et al., or Tai et al.*, in view of *Abe et al.* Applicants respectfully assert that none of these references can be combined to teach Applicants' invention.

All of these references, except for *Abe et al.* have already been discussed. The failure of these references to disclose or even suggest the use of cysteine protease as a vaccine renders their combination with any or all of the other secondary references inappropriate since there is no motivation to do so. As discussed in regards to Applicants prior arguments in this response, the mere purification and sequencing of a protein is inadequate to teach the creation of a vaccine. For example, there is no indication the dialysis procedure described in one of the references yields a nontoxic carrier, and no indication that such compound will yield a vaccine. In addition, the limitation that the vaccine compositions contain a physiologically acceptable vehicle in addition to the cysteine protease is ignored. The CCPA has held that "absent a disclosure by [the cited prior art] of specific therapeutic or pharmaceutical uses for [a known

compound], the addition of a pharmaceutical carrier to that compound and the determination of suitable unit dosage forms is not obvious." *In re Anthony*, 162 USPQ 594, 597 (CCPA 1969). Further, the claim requires that a conserved cysteine proteas be present in an amount sufficient to confer immunity to group A streptococcal infection, which is the *de facto* definition of a vaccine. None of the cited references describe either the conserved cysteine protease in combination with the physiologically acceptable vehicle, or a composition comprising the conserved cysteine protease in the specified amount. These limitations are not obvious variants of the cysteine proteases described in the cited prior art.

None of the references provide motivation to administer cysteine protease to a human or animal. Thus, there is no motivation in the cited prior art to incorporate the cysteine protease into pharmaceutically acceptable carriers in amounts sufficient to induce immunity against group A Streptococcal infection.

Most importantly, *Abe et al.*, does not teach using cysteine proteases as vaccines or methods of vaccination. *Abe et al.* discusses the toxic effect of speB toxin among others. In particular, *Abe et al.* discusses how speB acts as a superantigen and how this contributes to its function as a toxin. This toxic mechanism involves stimulation of immune cells that contribute to and accentuate the deleterious effects of the toxin. (See p.3750). This is completely unrelated to the suitability of speB as an immunizing agent. In fact, this teaching would lead one away from considering speB as a viable candidate for an immunization agent. Therefore *Abe et al.* could **never** be combined with another reference to yield a vaccine.

Furth rmore, there is considerable evidence that Applicants' invention is not obvious. Prior to Applicants' invention, no one has disclosed an effective vaccine against Group A Streptococcal infection, despite the dire need to develop one. For xample, over six million children were estimated to suffer from rheumatic heart disease in India alone in 1981. (Agarwal, *Lancet* 1:910, 1981). In the U.S., Group A Streptococcal infection causes about 25-35 million cases of pharyngitis per year, with costs of about $1-2 billion per year in direct health care costs. (*Fischetti et al.*, 240 *Science* 1487 (1981)). The grave nature of the illness caused by streptococcus coupled with the complete lack of an acceptable vaccine prior to Applicants' invention is strongly probative of nonobviousness. *In re Dow Chem. Co.*, 5 USPQ 2d 1529 (Fed. Cir. 1991) ("Recognition of need, and difficulties encountered by those skilled in the field are classical indicia of unobviousness.")

Claims 6-17 are rejected under 35 U.S.C. 103(a) as being unpatentable ov r *Fischetti et al.* and *Kehoe* in view of *Kapur I* or *II*, *Tai et al.*, *Hauser et al.*, *Gerlach et al.*, and further in view of *Abe et al.* In addition to the remarks that follow, Applicants refer the Office to arguments made earlier in this response regarding these various references.

The Office Action does not point out a single suggestion to combine any of these references. The Office Action must specifically point out the suggestions to combin references, it can not merely select bits and pieces from various references and provide 20-20 hindsight recombinations to yield Applicants' invention. In the instant case, even if the use of 20-20 hindsight was permitted, the references cited do not even provide the "parts" that can be combined to create Applicants' invention.

Fischetti et al. can not b combin d with any other reference to teach Applicants' invention. *Fischetti et al.* constructed a vaccina virus recombinant that expressed the conserved region of the structural gene encoding the M6 molecule, which is not a cysteine protease. *Kehoe* is a review article that reviews prior studies related to the development of group A streptococcal vaccines *using M protein* which is different than the cysteine protease of the instant invention. Furthermore, *Kehoe et al.* state that attempts to develop a Group A streptococcal infection vaccine have not been successful:

> **It may, however, be some time before an effective vaccine that could protect against a wide range of group A streptococcal M types will be produced, or even demonstrated to be feasible. It is clear that further studies are required.**[1]

Additionally, though *Kehoe et al.* may constitute an invitation to develop a Group A streptococcal infection vaccine, it fails as a § 103 reference because it does not suggest the means disclosed by Applicants to accomplish that end. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986).

As mentioned previously, *Abe et al.* investigates streptococcal erythrogenic toxin **mechanisms**, therefore, it can not be combined with any other reference to yield Applicants' invention.

As discussed previously, *Kapur et al.* investigates the role of cysteine protease in Group A streptococcal infection pathogenesis, but provides no suggestion of its use as a vaccine. Therefore, it is clear that none of the references cited in the Office Action can be combined to yield Applicants' invention.

In light of these remarks, Applicants respectfully request that the objections to th specification and the rejections of Applicants be reversed.

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[1] *Kehoe et al.* at 806.

Applicants assert that in light of the above remarks, the Application is now in condition for allowance. Accordingly, Applicants respectfully request that a Letter Patent be issued on the application. If any outstanding issues remain, please contact Thomas D. Paul at (713) 651-5325 for quick resolution.

Applicants do not believe that any additional fees are due. If, however, additional fees are due, please charge the additional fees to the deposit account of Fulbright & Jaworski L.L.P., Account No. 06-2375, under Order No. 957111, from which the undersigned is authorized to draw.

Respectfully submitted,

Date: 10/13/98

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